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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/797,841	03/10/2004	Antoine Michel Alain Bril	P32088C3	5685

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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 06/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/797,841	BRIL ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-7 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 10 March 2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. PCT/GB99/02361.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1 sheet.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Informalities

Claims 1-7 are currently pending and are the subject of this Office Action

Priority

Applicant's claim for the benefit of prior-filed foreign applications under 35 U.S.C. 119(e) is acknowledged. This application is a continuation of Application No. 10/290,596, filed November 8, 2002, now abandoned, which is a continuation of Application No. 10/072,098, filed February 7, 2002, now abandoned, which is a continuation of Application No. 09/744,124, filed January 19, 2001, now abandoned, which is a 371 of International Application No. PCT/GB99/02361 filed July 21, 1999.

The earliest effective U.S. filing date for the instant application has been determined to be February 7, 2002. The '124 application was abandoned on November 14, 2001 for failure to respond to an Office Action. As no request for Extension of Time was filed, continuing application '098 (filed February 7, 2002) was not co-pending with application '124 at the time of filing. Therefore, the claim of benefit and priority to prior filed foreign applications is not granted, as the '098 application was not a proper continuing application of the '124 application.

Double Patenting - Statutory

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor..." (Emphasis

added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 3 is rejected under 35 U.S.C. 101 as claiming the same invention as that of Claim 1 of prior U.S. Patent No. 6,613,785. This is a double patenting rejection.

Double Patenting - Nonstatutory

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 4-6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 2-4 of U.S. Patent No. 6,613,785. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant Claim 4 is dependent on instant Claim 3, thereby making dependent Claims 5 and 6 drawn to identical subject matter as claimed in the '785 patent.

Claim Objections

Claims 1 and 2 are objected to because of the following informalities: recitation of "selected from the list consisting of" is colloquial. Amending the claims to recite, "selected from the group consisting of" will overcome this objection. Appropriate correction is required.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) The quantity of experimentation necessary,

2) The amount of direction or guidance provided,

3) The presence or absence of working examples,

4) The nature of the invention,

5) The state of the prior art,

6) The relative skill of those in the art,

7) The predictability of the art, and

8) The breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth below:

1. The nature of the invention

The claimed invention relates to methods of reducing or preventing apoptosis of cells by administering a "glucose uptake enhancer".

2. State of the prior art

There are examples in the prior art of methods of reducing apoptosis and post-ischemic injury by administering thiazolidinediones, for example. The prior art also discloses other compounds that can be used for the same purpose.

3. Relative skill of those in the art

The relative skill of those in the art is generally that of a Ph.D. or M.D.

4. Predictability of the art

The treatment of post-ischemic injury and the reduction of apoptosis are unpredictable arts, especially given the limitation that the agent to be used in the treatment is a "glucose uptake enhancer". Every agent and even classes of agents will have different solubility properties and pH dependencies that can affect their dissolution rates, and therefore bioavailability. Further, it is impossible to foresee whether any and all compounds that can act as glucose uptake enhancers will also demonstrate a reduction of cell apoptosis.

Given the above, it is clear that the art to which the instant invention relates involves a relatively high degree of unpredictability.

5. Breadth of the Claim

Claims 1-2 are drawn to methods of reducing or preventing apoptosis by administering any "glucose uptake enhancer".

6. The amount of direction or guidance provided

The specification provides general guidance and background regarding the use of thiazolidinediones, a specific class of glucose uptake enhancers, in methods of

reducing post-ischaemic injury of the heart. On Page 6 of the Specification, Applicants state "As used herein 'glucose uptake enhancer' means an agent which increases basal or insulin-stimulated uptake of glucose across the cell membrane." The only class of glucose uptake enhancers specifically discussed and demonstrated are thiazolidinediones, specifically Compound (I).

7. Presence or absence of working samples

The only working example present in the disclosure is the use of Compound (I) in the recovery of post-ischemic hearts. No examples are provided regarding the use of glucose uptake enhancers in the reduction or prevention of apoptosis.

8. The quantity of experimentation necessary

The skilled artisan would expect that reducing or preventing apoptosis of differentiated cells would be complex and be affected by numerous parameters, including the biological profile of the actives, pH, the dissolution profiles of the actives, etc. and therefore, highly unpredictable. The instant specification sets forth no criteria for extrapolating beyond the one method actually demonstrated; nor does it give any guidance on how one would select and test a "glucose uptake enhancer" for reduction or prevention of apoptosis as recited in Claims 1-2.

Thus, the specification fails to enable one of ordinary skill in the art to use the methods of Claims 1-2.

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 and 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as follows:

In Claims 1-2 and 4-6 there is no antecedent basis for the first recitation of "...the human".

Claim 5 is not complete; it does not recite the name or structure of "Compound (I)". Amending the claim to recite the name or structure of Compound (I) will overcome this rejection, provided there is support in the Specification for such an amendment.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsui *et al.* (U.S. Patent No. 6,087,384; Issued July 11, 2000). The reference teaches compositions comprising thiazolidinediones and specifically teaches the thiazolidinedione, 5-(4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione (Compound I), of the instant claims (see especially Column 10, Lines 22-24). The reference also teaches that troglitazone, as recited in instant Claim 6, is useful in the methods described therein (Column 10, Lines 38-40). The reference further teaches that these compounds are insulin sensitizing agents (See especially Column 1, Lines 45-48), apoptosis inhibitors (see Abstract), and can be used in

methods to treat diseases mediated by promotion of apoptosis, including ischemic and neurodegenerative diseases (see especially Column 13, Lines 10-12 and 15-26). The pharmaceutical compositions disclosed in the reference can be administered from one to three times per day in doses of 0.1 to 30 mg/kg (Column 13, Lines 27-36), *i.e.* "acute administration".

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 99/59586 (Published November 25, 1999). The reference teaches that thiazolidinediones inhibit cardiomyocyte apoptosis following acute myocardial infarction (Abstract and Page 3, Lines 21-24), reduce insulin resistance (Page 3, Lines 18-19), improve glucose intolerance (Page 3, Line 20), and can be used in methods to improve cardiac function after acute myocardial infarction (see especially Abstract and Page 3, Lines 21-24). The reference further teaches the thiazolidinedione, 5-(4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione (Compound I), of the instant claims (see especially Page 20, Line 24) as being a preferred agent in the methods described therein. Thiazolidinediones recited in instant Claim 6 are also taught by the reference (see especially Page 20) as being useful in the methods described therein. The thiazolidinediones described in the reference can be administered to a mammal in an "effective amount" as instantly claimed (Page 4, Lines 18-22). The pharmaceutical composition recited in instant Claim 7 is disclosed by the reference on pages 25-26 wherein it is taught that the compounds can be used in "pharmaceutical preparations"

and administered from 0.1 to 50 mg/kg per day either singly or in a divided dose (*i.e.* "acute administration").

Claims 3-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwartz (U.S. Patent 5,968,960; Issued October 19, 1999). Schwartz teaches the thiazolidinediones recited in the instant claims (Column 10, Line 37 through Column 11, Line 25) are insulin sensitizers useful in enhancing resistance to myocardial ischemia associated dysfunction (see especially Abstract). The reference teaches the compounds can be administered acutely (Column 12, Lines 29-40), as instantly claimed, and that treatment of myocardial ischemia can be accomplished by administration, to a mammal, preferably human, suffering or susceptible to myocardial ischemia, an effective amount of an insulin sensitizer (Column 3, Lines 45-50).

Claims 3-4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Shimabukuro *et al.* (Applicant IDS Reference "AK"; Published 1996). The reference teaches that troglitazone, a thiazolidinedione recited in instant Claim 6, shows hypoglycemic effects in insulin-resistant animal models and humans (see especially Abstract). The reference further teaches that this compound improved post-ischemic functional deficits of diabetic hearts (Abstract).

With regard to the above rejections under 35 U.S.C. 102, thiazolidinediones are known in the art to enhance insulin-stimulated glucose uptake into peripheral tissues,

including skeletal muscle as evidenced in Soo Park *et al.* (J. Clin. Endrocrinol. Metab., 1998, 83:1636-1643). The Soo Park reference is cited only for evidentiary purposes to demonstrate that enhancing glucose uptake is an inherent property of Compound I and related thiazolidinediones.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2 and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shimabukuro *et al.* (Applicant IDS Reference "AK"; Published 1998) in view of Schwartz (U.S. Patent 5,968,960; Issued October 19, 1999).

Shimabukuro *et al.* disclose that apoptosis is increased in prediabetic and diabetic animal models of the disease (see especially Abstract, Page 2501, and Discussion). They further disclose that troglitazone, a thiazolidinedione recited in instant Claim 6, reduced apoptosis of pancreatic β-cell islets (see especially Page 2501, First Paragraph). The instant claims differ over the reference in reciting a method for reducing or preventing apoptosis, a specific thiazolidinedione compound (Compound (I); Claim 5), and a composition comprising said compound for acute administration.

Schwartz discloses the thiazolidinediones recited in the instant claims (Column 10, Line 37 through Column 11, Line 25) as being insulin sensitizers useful in enhancing resistance to myocardial ischemia associated dysfunction (see especially Abstract). The reference further teaches the compounds can be administered acutely (Column 12, Lines 29-40).

Given the disclosures of the above references, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the thiazolidinediones as recited in the instant claims in compositions to reduce apoptosis in the differentiated cells recited in instant Claim 1 as well as to reduce or prevent apoptosis of cells wherein the apoptosis was induced by ischemic insult, for example.

The skilled artisan would be imbued with at least a reasonable expectation of success given the disclosures of Schwartz and Shimabukuro.

With regard to the above rejection under 35 U.S.C. 103, thiazolidinediones are known in the art to enhance insulin-stimulated glucose uptake into peripheral tissues, including skeletal muscle as evidenced in Soo Park *et al.* (J. Clin. Endrocrinol. Metab., 1998, 83:1636-1643). The Soo Park reference is cited only for evidentiary purposes to demonstrate that enhancing glucose uptake is an inherent property of Compound I and related thiazolidinediones.

Conclusion

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James D. Anderson
Examiner
Art Unit 1614

JDA
May 2, 2006

Ardin H. Marschel 5/27/06
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER